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Iron supplements: a common cause of drug interactions

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Iron-drug interactions of clinical significance may occur in many patients and involve a large number of therapies. Concurrent ingestion of iron causes marked decreases in the bioavailability of a number of drugs. The affected drugs, tetracycline, tetracycline derivatives (doxycycline, methacycline and oxytetracycline), penicillamine, methyldopa, levodopa, carbidopa and ciprofloxacin have diverse chemical structures and clinical effects. The major mechanism of these drug interactions is the formation of iron-drug complexes (chelation or binding of iron by the involved drug). A large number of other important and commonly used drugs such as thyroxine, captopril and folic acid have been demonstrated to form stable complexes with iron. There is little known about the effects of concurrent therapy with iron supplements for most of the drugs.

Keywords iron drug interaction

Introduction

Patients are frequently treated with several drugs and commonly ingest over-the-counter pharmaceuticals. When patients ingest two or more drugs concurrently, there is a possibility the drugs will interact. Iron supplements are among the most frequently prescribed drugs (La Piana Simonson, 1989) and are taken in over-the-counter preparations by many more people. Iron compounds have been shown to cause marked reduction in the absorption of tetracycline (Neuvonen *et al.*, 1970), the tetracycline derivatives doxycycline, methacycline and oxytetracycline (Neuvonen *et al.*, 1970), as well as penicillamine (Osman *et al.*, 1983), methyldopa (Campbell *et al.*, 1988), levodopa (Campbell & Hasinoff, 1989; Campbell *et al.*, 1990a), carbidopa (Campbell *et al.*, 1990c) and ciprofloxacin (Polk *et al.*, 1989). The major mechanism by which iron interacts with these drugs is the formation of iron-drug complexes (Campbell *et al.*, 1988, 1990a,b; Campbell & Hasinoff, 1989; Neuvonen *et al.*, 1970; Osman *et al.*, 1983; Polk *et al.*, 1989). The formation of the iron-drug complexes reduces the extent of drug absorption and does not appear to reduce the rate of drug absorption (Campbell & Hasinoff, 1989; Campbell *et al.*, 1990c; Neuvonen *et al.*, 1970; Osman *et al.*, 1983; Polk *et al.*, 1989). Iron can also catalyze oxidation and reduction reactions (Southorn & Powis, 1988) potentially destroying drugs (Campbell *et al.*, 1990c). Iron catalyzed oxidation of carbidopa occurs *in vitro* (Campbell *et al.*, 1990c). Iron preparations can also alter drug metabolism *in vivo* as evidenced by methyldopa (Campbell *et al.*, 1988). A large number of drugs (Table 1) have functional chemical groups in a configuration which will result in stable iron-drug complexes. Many of these drugs have been shown to bind iron (Table 1) or other transition metals strongly (Table 2). Iron preparations are likely to reduce the absorption of several of these drugs. This manuscript reviews chemical and pharmacological factors likely to be involved in the iron-drug interactions, as well as the drugs currently demonstrated to have reduced bioavailability in the presence of iron.

Table 1 A partial list of orally administered drugs which bind iron

Paracetamol (Mayadeo & Banavali, 1986)
Ampicillin (Abd *et al.*, 1984)
Captopril (*)
Carbidopa (Campbell *et al.*, 1990c)
Ciprofloxacin (Polk *et al.*, 1989)
Ethambutol (Cole *et al.*, 1981; La Croix & Cerutti, 1987)
Folic acid (Nazarov *et al.*, 1981)
Indomethacin (Sanghavi & Sivanand, 1978)
Isoprenaline (Fujita *et al.*, 1985)
Levodopa (Campbell *et al.*, 1989)
Methyldopa (Abd *et al.*, 1984; Campbell *et al.*, 1990b)
Minoxidil (McCall *et al.*, 1987)
Nalidixic acid (Timmers & Sternglanz, 1978)
Norfloxacin (Issopoulos, 1989)
Penicillamine (Millar, 1981; Osman *et al.*, 1983)
Rifampicine (Barza, 1973)
Tetracycline (Albert & Rees, 1956; Gothoni *et al.*, 1972)
Thyroxine (Collange & Paris, 1983,*)
Salicylic acid (Fujita *et al.*, 1985)

*Campbell and Hasinoff unpublished data.

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Table 2 A partial list of orally administered drugs which have the potential to bind strongly to iron based on binding copper or on functional groups present

Antazoline
Bephenium
Chlorpheniramine
Cyclosporine
Dicumarol (Callester *et al.*, 1970; McElnay *et al.*, 1979)
Digoxin (Gajewska *et al.*, 1981)
Diethylstilbestrol
Diphenhydramine
17-Ethinyloestradiol
Frusemide (Callester *et al.*, 1970)
Hexylresorcinol
Methotrexate (Rowowsky *et al.*, 1986)
Oxazepam (Gajewska *et al.*, 1981)
Pheniramine
Thonzylamine

Chemical factors influencing the iron-drug interaction

The stability constant (K_s) of the iron-drug complex (Figure 1) is an indication of the strength of iron binding to drug and is a measure of the relative amount of bound and free drug (Brown, 1985; Pitt & Martell, 1980). Functional chemical groups on drugs to which iron strongly binds contain oxygen, nitrogen or sulphur (Pitt & Martell, 1980). These functional groups have electron pairs which may interact with ferrous or ferric ions forming coordinate or ionic bonds (Pitt & Martell, 1980). Functional chemical groups on drugs that are known to bind strongly to iron include phenolic, catechol, carboxyl, amine and sulphydryl groups (Abd *et al.*, 1984; Campbell & Hasinoff, 1989; Campbell *et al.*, 1990b; Collange & Paris, 1983; Millar, 1981; Pitt & Martell, 1980). Many of these functional groups are weak acids and thus the binding of iron to drugs with these groups is highly pH dependent (Figure 1). Strong binding to iron (high stability constants) occurs when more than one functional group on a drug binds iron (Brown, 1985; Day & Underwood, 1974). Most drugs which bind iron ions bind two functional groups. These complexes are most stable when the binding results in a five or six membered ring consisting of iron, the functional groups involved in binding and other intervening atoms. Iron has a co-ordination number of six indicating its strong tendency to bind six functional groups (Brown, 1985). Typically, one, two or three drug molecules bind one iron ion. Complexes with a high drug:iron ratio may result in a relatively small quantity of iron binding a considerably greater quantity of drug. The ferric form of iron generally binds much stronger to compounds than the ferrous form due to its higher positive charge (Campbell & Hasinoff, 1989; Campbell *et al.*, 1990b). Therapeutically, iron is generally used in the ferrous form (Hillman & Finch, 1985; Pitt & Martell, 1980), but can rapidly oxidize to the ferric form under conditions similar to those present in the gastrointestinal tract (Campbell & Hasinoff, 1989). The stability constant can be predicted reasonably accurately by an inspection of the drug structure and application of these principles. Iron-drug complexes with high binding constants may have an increased likelihood of iron-drug interactions as there will be a lower concentration of the free drug available for absorption.

$$ {}_n\text{HDRUG} + \text{Fe}^{3+} \rightarrow \text{Fe}^{3+}(\text{DRUG}^-)_n + n\text{H}^+ $$

$$ K_s = \frac{[\text{iron-drug}_n\ \text{complex}]}{[\text{iron}] \times [\text{drug}]^n} $$

Figure 1 The chemical reaction between an acidic drug and the ferric form of iron resulting in the formation of an iron-drug complex. The stability constant (K_s) is calculated from the concentrations of unbound drug, unbound iron and iron-drug complex at equilibrium as shown.

The solubility of the iron-drug complexes in aqueous solutions (e.g. gastrointestinal fluids) is another factor which may affect the extent of the iron-drug interaction. The binding of drugs to iron ions may result in soluble complexes or insoluble precipitates (Albert & Rees, 1956; Brown, 1985). Precipitation of the iron-drug complex would result in less drug being available for absorption. The water solubility of the iron-drug complex is often related to the net charge on the complex but is difficult to predict based on an inspection of the drug structure. All the currently documented iron-drug interactions in the gastrointestinal tract show decreases in drug absorption, however it is also possible that lipid soluble iron-drug complexes could be absorbed to a similar or greater extent than the parent drug (Rajan *et al.*, 1976). If a drug has low lipid solubility and is poorly absorbed and the iron-drug complex is more lipid soluble, this could lead to increased drug delivery. Ascorbic acid and some amino acids form complexes with iron and this results in an increase in iron absorption (Conrad & Schade, 1968) while tetracycline administration with iron reduces iron absorption (Greenberger *et al.*, 1967).

Clinical pharmacology of the iron-drug interaction

Most of the drugs documented to have reduced bioavailability in the presence of iron are those which are incompletely absorbed. Levodopa is an exception to this statement, however multiple factors can reduce levodopa absorption (Nutt & Fellman, 1984) suggesting the gastrointestinal tract has a limited 'reserve' to absorb levodopa. Drugs which undergo enterohepatic cycling may also be more susceptible to this interaction as drug will be repeatedly exposed to iron in the gastrointestinal tract.

The quality of iron ingested relative to the drug dose is an important variable affecting the iron-drug interaction. Multiple daily doses of approximately 60 mg of 'elemental' iron are usually used in iron replacement therapy while the 'elemental' iron content of multivitamin tablets (with iron) varies from 2 to 105 mg (Hillman & Finch, 1985; Krogh, 1989). The higher the iron concentration relative to the drug, the more drug will be bound.

The timing of ingestion of iron and drug is important. For convenience, patients frequently ingest drugs together. Drug-iron interactions are significant when iron is taken within 2–3 h of tetracycline (Gothoni *et al.*, 1972) and methyldopa (Campbell, unpublished data) but studies are necessary with other drugs to determine if they are similarly affected. Multivitamin tablets with iron are usually taken once a day (Krogh, 1989) and may result

in clinically significant interactions with other therapies administered in a single daily dose. Multivitamin tablets also frequently contain copper and zinc ions which also form complexes with drugs (Table 1). Drugs which are taken frequently during the day will be less likely to interact clinically with iron in vitamin tablets but may be affected by the multiple daily doses of iron generally used in therapy of iron deficiency (Hillman & Finch, 1985; Krogh, 1989). Current trends in drug development are towards once a day drug therapy and may increase susceptibility to the iron-drug interaction.

Patients frequently ingest several medications at the same time or with meals and this may influence the extent of iron-drug interactions. The binding of most drugs to iron is pH dependent, therefore drugs and food which effect gastrointestinal pH will alter iron-drug binding and may therefore influence the extent of the interaction between iron and other drugs. Drugs such as histamine H_2-receptor blockers, and antacids increase gastric and upper small intestine pH and will likely increase the interaction between iron and drugs with acidic functional groups. The influence of food on iron-drug interactions is unknown. Foods have the potential to bind iron and may potentially decrease iron-drug binding. Although some foods contain significant quantities of iron (Krogh, 1989), this is less likely to result in significant iron-drug complex formation. The iron content is substantially lower in food than pharmacologic preparations and the binding of iron to drug will have to compete with iron binding to food.

Occasionally drugs and iron are prescribed in slow-release formulations (Hillman & Finch, 1985; Krogh, 1989). The effect of these formulation on drug-iron interactions is not well documented but it is likely that slow-release formulations of iron or drug will influence iron-drug binding. Slow-release drug preparations may be more susceptible to iron binding as at any given time there will be less free drug. For similar reasons, slow-release iron preparations may result in less drug binding by lowering the iron : drug ratio. Iron formulations which dissolve slowly cause a smaller decrease in tetracycline absorption than faster dissolving iron preparations (Florance & Attwood, 1988). If the slow-release preparations have different gastrointestinal transit time than the ordinary tablets, then there may be decreased iron-drug binding under all situations.

Known iron-drug interactions

Several drugs have reductions in bioavailability when ingested with iron preparations. The drugs have different clinical effects and chemical structure (Figure 2).

Tetracyclines Tetracyclines are broad spectrum antibiotics in use since the late 1940s (Sande & Mandell, 1985). Iron has been shown to bind to tetracycline and its derivatives (Albert & Rees, 1956). The binding of the ferrous form of iron to tetracycline is only moderately strong (log K_s 9.3) but results in the formation of a precipitate with a complex of two tetracycline molecules to one iron ion (Albert & Rees, 1956). Iron in its ferrous form can also rapidly oxidize to the ferric form under conditions similar to those in the gastrointestinal tract (Campbell & Hasinoff, 1989). The ferric form of iron

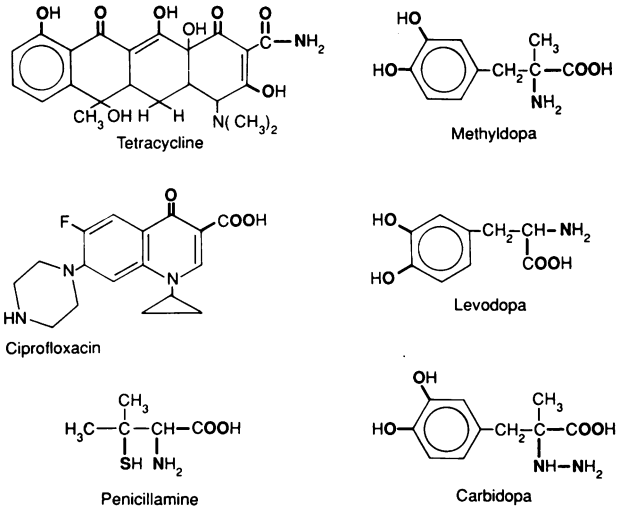

Figure 2 The chemical structures of drugs which have been demonstrated to have reductions in bioavailability when ingested with iron compounds. The functional chemical groups which may bind iron are in bold.

binds tetracycline and its derivatives to iron in its ferric state very strongly with a log $K_s > 20$ (Albert & Rees, 1956). About 20 years after the introduction of tetracyclines, the concurrent administration of tetracycline with ferrous sulphate was shown to decrease the absorption of tetracyclines (Neuvonen *et al.*, 1970). Tetracycline plasma levels are reduced approximately 50% while some of its derivatives have plasma levels reduced as much as 80–90% by coadministration of 200 mg of ferrous sulphate (Neuvonen *et al.*, 1970). Other iron salts have also been shown to decrease tetracycline levels (Florance & Attwood, 1988). Faster dissolving iron preparations interfere with tetracycline absorption to a greater extent than slower dissolving preparations (Florance & Attwood, 1988). Administration of iron 3 h before or 2 h after tetracycline avoids the decreases in tetracycline levels (Gothoni *et al.*, 1972).

Penicillamine Penicillamine is a drug used in the treatment of rheumatoid arthritis as a second line remittive agent, and has also been used as a chelator in heavy meal intoxication, in cystinuria where the drug increases cystine solubility and as the treatment of choice in Wilson's disease, a rare copper storage disease (Klaassen, 1985). Penicillamine has been in use since the late 1950s. Penicillamine binds strongly to transition metal elements, e.g. zinc (log K_s 22.7) (Gergely & Sovago, 1979; Strand *et al.*, 1983). Both ferric and ferrous forms of iron form complexes with penicillamine in the ratio of two drug molecules to one iron ion (Gergely & Sovago, 1979; Strand *et al.*, 1983). Administration of penicillamine with iron was shown to cause a decreased absorption of penicillamine (Osman *et al.*, 1983). The bioavailability of penicillamine is reduced 80% by 300 mg of ferrous sulphate and peak levels are reduced 67% (Osman *et al.*, 1983). It has been suggested that iron preparations may reduce penicillamine toxicity (Lyle, 1976) but it is likely this is due to a reduction in penicillamine bioavailability which will also reduce penicillamine efficacy.

Methyldopa Methyldopa has been used as an antihypertensive agent since the late 1950s. In 1988 it was still one of the 100 most commonly prescribed drugs in the United States (La Piana Simonson, 1989). The ferric form of iron binds strongly to methyldopa with a log K_s of 18 (Abd *et al.*, 1984). Methyldopa has been shown to increase the rate of oxidation of ferrous iron to its ferric form (Campbell *et al.*, 1990b). Studies performed almost thirty years after the introduction of methyldopa have shown a marked decrease in bioavailability of methyldopa when it is ingested with ferrous sulphate or ferrous gluconate (Campbell *et al.*, 1988, 1990b). Absorption of methyldopa was reduced by 73% with 325 mg of ferrous sulphate and by 61% with 600 mg of ferrous gluconate (Campbell *et al.*, 1988). Due to dose dependent metabolism of methyldopa (Campbell *et al.*, 1984) there was an 88% and 79% decrease in renal excretion of unmetabolized methyldopa with concurrent ferrous sulphate and ferrous gluconate respectively (Campbell *et al.*, 1988). The decrease in bioavailability appears to affect adversely blood pressure control in patients treated with methyldopa (Campbell *et al.*, 1988). Studies have shown that giving ferrous sulphate 1 and 2 h before methyldopa still has a significant effect on methyldopa absorption ($n = 4$, 83% decrease at 0 h, 55% decrease at 1 h and 42% decrease at 2 h, Campbell, unpublished data).

Levodopa and carbidopa Levodopa has been the main form of therapy for Parkinson's disease since the early to mid 1970s (Yahr & Bergman, 1987). Levodopa has a similar structure to methyldopa and also complexes with iron in its ferrous and ferric states (Campbell & Hasinoff, 1989; Hillman & Finch, 1985). Levodopa and methyldopa increase the rate of oxidation of iron from its ferrous to the ferric state (Campbell & Hasinoff, 1989). The ferric form of iron binds levodopa strongly (Campbell & Hasinoff, 1989). Levodopa and the ferric form of iron form a 3:1 levodopa:iron complex (Campbell & Hasinoff, 1989). Administration of ferrous sulphate with levodopa leads to a 51% decrease in levodopa bioavailability (area under the plasma levodopa concentration curve (AUC) and a 55% decrease in peak levels in healthy subjects (Campbell & Hasinoff, 1989). A study examining the effect of ferrous sulphate on Sinemet (a combination of levodopa and carbidopa) therapy in patients with Parkinson's disease (Campbell *et al.*, 1990c) found a 30% reduction in levodopa AUC and a 47% reduction in peak levodopa levels. The reductions in levodopa bioavailability were associated with deterioration in patients' disability from Parkinson's disease ($r_s = 0.833$, $P > 0.01$). There was a greater than 75% reduction in carbidopa bioavailability when ferrous sulphate was ingested with Sinemet. Chemical studies demonstrated that carbidopa was both bound and oxidized by iron. Carbidopa increases the oxidation of the ferrous form of iron to its ferric form in a manner similar to methyldopa and levodopa. The ferric form of iron binds carbidopa strongly (Campbell *et al.*, 1990c).

Ciprofloxacin Ciprofloxacin is a recently released quinolone antibiotic. A variety of divalent and trivalent cations form complexes with quinolones likely by binding the 3-ketone and 4-carboxylic acid group (Polk *et al.*, 1989; Timmers & Sternglanz, 1978) (Figure 3). The administration of ferrous sulphate 300 mg with ciprofloxacin causes a 75% reduction in peak ciprofloxacin concentrations and a 64% reduction in ciprofloxacin bioavailability (Polk *et al.*, 1989). Administration of a multivitamin tablet containing transition metal zinc (23.9 mg) and copper (4 mg) caused a 24% reduction in ciprofloxacin bioavailability (Polk *et al.*, 1989). Other quinolone antibiotics also have the 3-ketone and 4-carboxylic acid functional groups and will likely be affected to a similar extent by iron supplements.

A large number of important and commonly used drugs form stable complexes with iron, however, little is known about the clinical consequences of this binding. All the published iron-drug interactions have shown marked reductions in drug bioavailability. It is possible that there are many more iron-drug interactions of clinical significance as a result of the formation of complexes and that many patients may receive inadequate therapy based on this mechanism. Further investigation is required to determine the clinical significance of chemical interactions between iron and drug molecules.

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